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Mechanisms of Radiation-Induced Conditioned Taste Aversion Learning

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RABIN, B. M. AND W. A HUNT. *Mechanisms of radiation-induced conditioned taste aversion learning*. NEUROSCI BIOBEHAV REV 10(1) 55–65, 1986.—The literature on taste aversion learning is reviewed and discussed, with particular emphasis on those studies that have used exposure to ionizing radiation as an unconditioned stimulus to produce a conditioned taste aversion. The primary aim of the review is to attempt to define the mechanisms that lead to the initiation of the taste aversion response following exposure to ionizing radiation. Studies using drug treatments to produce a taste aversion have been included to the extent that they are relevant to understanding the mechanisms by which exposure to ionizing radiation can affect the behavior of the organism.

Ionizing radiation Conditioned taste aversion Lithium chloride Area postrema Behavior

THE toxicity of ionizing radiation generally is expressed as the loss of rapidly turning over cells. This results from an impairment of the synthesis of these cells, especially those in bone marrow. However, since neurons in the mature central nervous system do not undergo cellular turnover, the brain generally has been believed to be insensitive to exposure to ionizing radiation [71], thereby allowing for the routine use of radiation in treating brain tumors. However, little attention has been given to evidence appearing over the years that raises doubts about this conclusion. For example, exposure to ionizing radiation at doses of 15–500 rad significantly reduces the electroshock seizure threshold, an effect lasting up to 8 months [97]. Also, in this dose range emesis is induced. Transient increases in the spontaneous locomotor activity of C57BL mice and arousal in rats have been observed after exposure to 1000–1500 rad [60,83]. And, on the molecular level, the functioning of sodium channels is impaired after radiation exposure to as little as 10 rad [140]. These observations suggest that exposure to ionizing radiation may have behavioral consequences not previously appreciated.

High lethal doses of ionizing radiation can severely disrupt behavior. Depending upon the species, the quality of radiation, and the nature of the behavioral measurements, 1000–10000 rad degrades performance on a number of tasks. Under some conditions the effects are transient, generally lasting up to one hr after irradiation [7, 14, 15, 36, 64], but after sufficiently high doses of radiation a permanent incapacitation is induced, culminating in the death of the organism. Possible effects of lower doses (<1000 rad) of radiation have not been adequately explored. Therefore, given the available evidence, such as that cited above, exposure to ionizing radiation may have subtle actions on the brain that may have clinical significance.

In addition to emesis, exposure to lower doses of ionizing radiation induces a conditioned taste aversion (CTA) in experimental animals and humans. A CTA can result when a novel tasting solution is paired with a toxin, so that when the solution is presented subsequently, further ingestion is avoided. This avoidance behavior is typically acquired after a single pairing of the solution with the toxin. Taste aversions can be produced, using saccharin or sucrose solutions, after injection of a wide variety of drugs, such as lithium chloride (LiCl), amphetamine, copper sulfate, and apomorphine [44,113], as well as after exposure to ionizing radiation [124]. Since radiation-induced taste aversions are obtained typically after exposure to 37–150 rad doses, examining the underlying mechanisms associated with development of this type of CTA might provide information on other possible behavioral consequences of low-dose irradiation. Such a model has the additional benefit of having an extensive behavioral and physiological database relating to taste aversions in general (see [1, 47, 117] for recent reviews of drug-induced CTA learning).

The goal of this paper is to review the variety of studies that have used radiation to produce a CTA in order to define the general mechanisms by which exposure to nonlethal levels of radiation might alter behavior. Our purpose is not to review CTA learning in general. However, studies with toxins in addition to radiation will be presented when they are relevant to the discussion.

A number of methods are used to produce a CTA. Since interpretation of information derived from some procedures

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can be misleading, we will begin with a brief discussion of the various methods employed for producing a CTA and their advantages and disadvantages.

METHODOLOGICAL CONSIDERATIONS

The general procedure for producing a conditioned taste aversion involves placing the subjects on a water deprivation schedule. Once the animal has adapted to the schedule, a novel tasting solution is substituted for the regular water bottle as the conditioned stimulus (CS). Ingestion of the novel solution is followed by treatment with the toxin, the unconditioned stimulus (UCS). The dependent measure, the conditioned response (CR), is the amount of the solution ingested at a subsequent presentation of the CS.

Within this general paradigm, a number of variations are used in quantifying the dependent measure, although the suggestion has been made that these different procedures may be measuring different aspects of CTA learning [131]. One such variation involves the use of either a one-bottle or two-bottle test to study taste aversion learning. In a single-bottle test, the animal is presented with only a single bottle containing the CS during the period in which fluid is available. In a two-bottle test, the animal can choose between the CS or a neutral fluid such as tap water. In a single-bottle test the subject is forced to choose between ingesting the solution that has been paired with the UCS or "going thirsty"; whereas with a two-bottle test, an alternative is available to drinking the CS.

A second variation in the dependent measure involves determining either the absolute or the relative intake. In a single-bottle test, the most typical dependent measure is the actual amount of the CS ingested by the subject, although postconditioning intake may also be expressed as a percentage of CS intake on the conditioning day prior to treatment. When a two-bottle design is used, the data are typically presented in terms of the relative intake of both the neutral and conditioned stimuli. While the data from a two-bottle test may be presented in terms of the actual intakes of each solution, the data can also be presented as a sucrose preference score, calculated by dividing the CS intake by total fluid intake. Because this preference measure is relatively insensitive to variations in total fluid intake, the preference score has been considered to be a more sensitive indicator of CTA learning [31,53], particularly under conditions in which the taste aversion produced by the UCS is relatively weak.

Using a single-bottle design may also introduce a potential conflict that can result from forcing the animal to ingest the solution which has been paired with the UCS. The only other alternative for the animal is not to drink at all. Conflict is not involved with a two-bottle design because the subject can choose which solution to drink. The introduction of conflict into the CTA learning paradigm can complicate the interpretation of data relating to possible mechanisms underlying CTA acquisition. This is a significant problem is studies that have attempted to assess a possible role of pituitary/adrenal hormones in CTA learning. In a series of studies using single-bottle designs, Smotherman *et al.* [128,129] have reported that acquisition of an LiCl-induced CTA is associated with the activation of the pituitary/adrenal system. Manipulation of corticosteroid levels by injection of ACTH or dexamethasone produces corresponding changes in the acquisition or extinction of the CTA response [56, 57, 127]. However, more recent work has shown that it is possible to dissociate the corticosteroid and behavioral responses to LiCl injection by varying the number of LiCl preexposures to which the animals are subjected [130]. This observation suggests that CTA acquisition is not dependent upon the LiCl-induced changes in pituitary/adrenal function. Consistent with this finding is the report by Rabin *et al.* [104] that hypophysectomy has no effect on the acquisition of an LiCl-induced CTA in rats tested using a two-bottle procedure.

Similar findings have been reported with radiation-induced taste aversion learning. Garcia and Kimeldorf [40] working with non-deprived rats in a single-bottle design reported that hypophysectomy had no effect on the acquisition of a radiation-induced CTA in rats. Similarly, Rabin *et al.* [104] found that hypophysectomy had no effect on radiation-induced CTA learning in rats tested with a two-bottle procedure. In contrast, Cairnie and Leach [16], using a single-bottle test with deprived animals, reported that injections of dexamethasone produced a significant attenuation of a radiation-induced CTA in rats. However, using a two-bottle test Rabin *et al.* (unpublished manuscript) found no effect of the drug. Since hormones of the pituitary/adrenal system have been shown to play a role in mediating conflict-induced arousal [55,138], these results suggest that activation of the pituitary/adrenal system or manipulation of corticosteroid levels in a CTA paradigm is related more to conflict produced using a single-bottle experimental design than to the CTA learning itself.

A second potential confounding artifact in studies attempting to evaluate the mechanisms involved in mediating CTA learning may result from a failure to control for the effects of state-dependent learning [94]. State-dependent learning results from a failure to maintain identical conditions (states) on both the conditioning and test days. Consequently, a CTA that is learned on the conditioning day is not recalled on the subsequent test day because the test conditions are different than the conditions under which the response was originally learned. In experiments designed to evaluate the effects of a variety of potentially disruptive treatments on CTA acquisition the usual procedure is to interpolate some treatment during the interval between the presentation of the CS and UCS on the conditioning day. Under these conditions, the subjects are exposed to the CS in the same treatment-free environment on both conditioning and test days. Some experimental manipulations, however, may require that the disruptive treatment be administered prior to, or coincident with, the presentation of the CS on the conditioning day. If the identical treatment is not subsequently administered together with the presentation of the CS on the test day, then the different conditions on the two days can interfere with the recall of the previously acquired CTA response. Under these conditions, identical treatments must be administered on both conditioning and test days to maintain identical states on both days.

That state-dependent learning can present a serious problem for studies designed to analyze the mechanisms of CTA learning has been shown by a number of studies using a variety of unconditioned stimuli and disruptive treatments. Working with ionizing radiation, Levy *et al.* [75] reported that treatment of rats with an antihistamine (chlorpheniramine maleate) on the conditioning day attenuated the acquisition of a CTA to saccharin. However, they administered the antihistamine prior to the initial exposure of the CS and failed to give a corresponding treatment on the test day. When the antihistamine is administered together with the CS on both conditioning and test days, treatment with the antihistamine has no effect on the acquisition of a radiation-

induced CTA [102]. Alternatively, when the antihistamine is given after the presentation of the CS, so that the animals are in a drug-free state on both conditioning and test days, neither intraperitoneal [16, 102, 119] nor intraventricular [101] injections of antihistamine have an effect on the acquisition of a radiation-induced CTA.

In addition to the use of a radiation UCS, state-dependent effects have also been observed in studies of drug-induced CTA learning. Phillips and LePiane [96] have reported that the disruption of LiCl-induced CTA learning produced by stimulation of the basolateral amygdala is not observed when that stimulation is given on both the conditioning and test day. Similarly, in a pilot experiment, Rabin and Hunt (unpublished manuscript) found that the reported disruption of an amphetamine-induced CTA by pretreatment with alpha-methyltyrosine [50] is greatly attenuated if the treatment sequence is administered prior to the presentation of the CS on both the conditioning and the test day. It would therefore seem that the problems posed by state-dependent learning are general, affecting a variety of unconditioned stimuli and disruptive treatments. As a result, appropriate controls for state-dependent effects must be employed where a disruptive treatment is administered prior to or during the presentation of the CS

THE RADIATION-INDUCED CTA

Some Parametric Considerations

Ionizing radiation is only one of many potential unconditioned stimuli which can be used to produce a CTA [44, 113, 124]. Therefore, it would be important to review some of the parametric factors associated with the acquisition of taste aversions produced by exposure to ionizing radiation or by injection of chemical compounds. A consideration of some of the similarities and differences in taste aversion learning produced by these various unconditioned stimuli will facilitate a comparison of the mechanisms involved in the acquisition of a CTA.

As indicated above, the dose of radiation used to produce CTA learning is well below the lethal dose [45,124]. Threshold doses for whole body exposures in rats have been variously reported to range from 7.5 rad [45] to between 20–25 rad [108]. These variations probably reflect differences in the radiation quality and in the conditions associated with the behavioral testing [124]. Further increases in the dose produce a non-linear increase in the strength of the aversion [108], such that whole body exposures of 50–100 rad produce a nearly total avoidance of the CS (e.g., [45, 124, 126]).

Similar results are obtained with LiCl. The threshold dose for an LiCl-induced aversion is between 0.15 and 0.30 mEq/kg [91,108]. Further increases in the dose of LiCl also produce a non-linear increase in the strength of the aversion, with the maximum aversion being reached with doses of 3 mEq/kg [91].

Amphetamine, in contrast to both radiation and LiCl, does not show this dose/response relationship. The threshold dose for amphetamine-induced CTA is between 0.5 and 1.0 mg/kg, but further increases in dose up to 2.0 mg/kg do not produce a corresponding increase in the strength of the aversion [108].

Despite the similar dose/response relationships between radiation and LiCl, there are significant differences in time-courses of the conditioning effects. This is primarily reflected in the capacity of the radiation UCS to produce a CTA when presented in a backwards conditioning paradigm [2]. A radiation-induced CTA can be acquired when the radiation UCS is presented up to 6 hr preceding the presentation of the CS. The strength of the aversion seems to be the greatest when the UCS precedes the CS y 90 min [19]. LiCl, in contrast, is not capable of inducing a CTA under these conditions. These observations indicate that exposing the organism to ionizing radiation, unlike treatment with LiCl, causes a long-lasting change that produces the temporal overlap necessary for the acquisition of a CR.

A related issue concerns the dose equivalence of different unconditioned stimuli when comparing their mechanisms of action. When a given treatment or manipulation shows an equivalent effectiveness in modulating a CTA produced by different unconditioned stimuli, the empirical observation is, by itself, sufficient evidence for a similarity of mechanism as it relates to those specific experimental conditions. In contrast, the observation that an experimental manipulation is effective in modulating a CTA produced by one UCS but not by another UCS may mean either that the mechanisms of action of these stimuli are different, or that there are differences in the initial effectiveness of those stimuli in producing a CTA. In part, the validity of the two hypotheses can be determined by comparing the experimental dose of the CTA-inducing agents with the threshold doses of those agents. In general, a given manipulation is less likely to be effective in modulating a CTA the greater the experimental dose is above the threshold dose (e.g., [35,110]). In addition, the two alternatives can be evaluated by comparing the effects of the manipulations on a variety of response measures. Thus, for example, LiCl- and amphetamine-induced aversions are different not only in terms of the effects of area postrema lesions on the acquisition of the response, but also in terms of the non-consummatory responses elicited by the two stimuli [95,114].

Role of Illness

One of the major unknowns in the acquisition of a radiation-induced CTA concerns the nature of the UCS. What are the specific characteristics of the UCS that lead to the subsequent avoidance of a "food" with which the UCS has been associated? With injections of toxic unconditioned stimuli that produce obvious signs of illness in the organism such as LiCl or copper sulfate, for example, a direct relationship is assumed between the gastrointestinal effects of the UCS and the resultant CTA learning [22, 23, 118]. Consistent with this hypothesis is the observation that lesions of the area postrema, the chemoreceptive trigger zone for emesis [9], disrupt the acquisition of a CTA produced by injections of methylscopolamine [4,114] and by injections of LiCl [103,114]. That the acquisition of a CTA requires a relatively specific UCS is shown by the observation that pairing a novel CS with a painful exteroceptive UCS, such as shock, does not readily result in CTA learning [41,73]. This observation which shows that pain *per se* is not an effective UCS for CTA learning suggests that the UCS may in some way involve the gastrointestinal system. However, even assuming, for the moment, that the toxic character of some stimuli constitutes the direct antecedent condition for CTA learning, a CTA can also be produced by pairing a novel CS with a variety of unconditioned stimuli (such as amphetamine, cannabinols, sesame oil and morphine) that are not only non-toxic, but will also be self-administered [3, 28, 38, 49]. This would suggest that the toxicity of a UCS is not a necessary condition for CTA learning to occur.

Whether the toxicity of radiation is important for the development of a CTA is not clear. As indicated in the preceding section, high doses of radiation (>500 rad) are clearly toxic stimuli which can produce a variety of changes in neural [67, 112, 136, 141] and behavioral [30, 82, 89, 90] functioning. In addition, like both LiCl and copper sulfate, irradiation can lead to emesis [8,12] and, in humans, to nausea [120]. In contrast, the dose of radiation (37–150 rad) typically used to produce a CTA, has no apparent effect on the unrestrained behavior of the organism [124]. However, lesions of the area postrema attenuate a radiation-induced CTA just as they attenuate a CTA following an injection of LiCl [93,103]. This might suggest that a radiation-induced change, possibly related to emesis, is a factor in the acquisition of a radiation-induced CTA, and that, therefore, there is some relationship between the toxic nature of radiation and the capacity of exposure to ionizing radiation to lead to CTA learning.

If an effect on the gastrointestinal system related to emesis does play a role in the acquisition of a CTA when a toxic UCS is used, then it should be possible to disrupt the CTA by treating the organisms with an antiemetic to prevent the development of the malaise. Initial experiments did not support the hypothesis of a link between the antiemetic-sensitive gastrointestinal distress and CTA learning. Levy *et al.* [75] reported that pretreating rats with the antiemetic trimethobenzamide did not disrupt the acquisition of a radiation-induced CTA, and Gadusek and Kalat [37] reported that treatment with scopolamine did not attenuate the recall of a previously acquired LiCl-induced CTA. However, reasoning that these previous investigations used doses of antiemetics that were much higher than the clinically effective doses, Coil *et al.* [23] tested the effects of several doses of a variety of antiemetics on the recall of a LiCl-induced CTA. They found that treatment with the clinically effective doses of scopolamine, trimethobenzamide, prochlorperazine and cyclizine produced a significant attenuation of the previously acquired CTA. Doses of antiemetics either greater or less than the clinically effective dose had no effect on CTA recall. These results would be consistent with the hypothesis that a UCS-induced illness plays a role in CTA learning when LiCl is used as the UCS.

More recent research however, has failed to confirm these findings. Goudie *et al.* [51], working with taste aversions produced by a variety of drugs including LiCl, reported that treatment with the clinically effective doses of scopolamine or prochlorperazine had no effect on the recall of a previously acquired CTA. In a more detailed study, Rabin and Hunt [99] looked at the effect of antiemetic treatment on both the acquisition and recall of taste aversions produced by injection of LiCl or by exposure to ionizing radiation. Treatment with the previously reported effective doses of trimethobenzamide, prochlorperazine or cyclizine [23] did not attenuate the acquisition of either a radiation- or LiCl-induced CTA. Because radiation exposure can produce a CTA when administered up to 6 hr prior to ingestion of the CS [2] and because the maximal effects of irradiation on CTA learning are observed 90 min after exposure [19], additional groups of rats were included in this study that were given one injection of prochlorperazine 15 min prior to irradiation or to injection of LiCl and a second antiemetic treatment 3 hr later. This extended antiemetic treatment, which would be expected to overlap the period of radiation effects, also had no effect on the acquisition of a CTA. As would be expected, given the lack of effect of antiemetic treatment on CTA acquisition, there were also no effects on the recall of a previously acquired radiation- or LiCl-induced CTA. In this part of the experiment the procedures used were similar to those of Coil *et al.* [23], which would suggest that any possible effect of antiemetic treatment on CTA learning is marginal at best. Consistent with this interpretation is the observation that, in humans, nausea is not a necessary symptom in subjects that acquire a CTA [5]. Therefore, the data do not provide compelling evidence that a UCS-induced illness is a direct antecedent condition to CTA learning.

The failure to find a consistent effect of antiemetic treatment on CTA learning produced by a toxic UCS raises some questions about the role of a UCS-produced illness as an antecedent condition to the acquisition of a radiation-induced CTA. Possibly the toxicity of the UCS is a side-effect of the treatment that is not required for the acquisition of the CTA. Some additional evidence is concordant with this possibility. Several studies have provided evidence which indicates that pairing a novel CS with the illness produced by various poisons is not, by itself, sufficient to produce a CTA [66,92]. Similarly, both radiation- and LiCl-induced taste aversions can be acquired by rats that are exposed to the UCS while under deep surgical anesthesia and maintained under the anesthesia for an additional 4–8 hr [100,116]. Under these conditions, it is difficult to understand how the experience of a possible UCS-induced illness could contribute to the acquisition of the CTA.

Role of the Gastrointestinal System

Even though the data on radiation presented above suggest the possibility of a subtle effect on nervous system function following exposure to low doses of ionizing radiation, these radiation-induced changes in nervous system activity do not seem to be critical for the occurrence of CTA learning [61]. Garcia and Kimeldorf [40] reported that radiation exposure restricted to the abdomen of rats could serve as the UCS for CTA learning. Although a higher dose of abdomen-only radiation is needed to produce an aversion equivalent to that produced by whole-body exposure, irradiation restricted to the abdomen is much more effective in producing a CTA than is irradiation restricted to the head, pelvis, or thorax alone. These basic results have been replicated in a number of investigations that, despite utilizing a variety of procedures, all show that body-only radiation exposure will produce a stronger aversion and at a lower dose than will head-only irradiations [106,126]. Since exposure of pelvis or thorax would be expected to affect the spinal cord and peripheral nerves to a similar extent as irradiation of the abdomen, the greater effectiveness of exposure of the abdomen in producing a CTA would be consistent with the hypothesis that some effect of the radiation related to the gastrointestinal system may be involved in mediating the acquisition of the radiation-induced CTA.

There are two possible mechanisms by which exposure of the abdomen can lead to taste CTA learning. First, the radiation may have a direct effect on the activity of the gastrointestinal system. Second, it may act as a nonspecific toxin causing the release of some humoral factor related to a generalized irritation of the gastrointestinal system. In support of the first possibility, Hulse and Mizon [58] have reported that exposing the abdomen of rats to ionizing radiation at doses of 20–100 rad produces a delay in gastric emptying which is correlated with the strength of an aversion to a

barium meal. Exposing the head and shoulders of rats to radiation doses of up to 200 rad does not have an effect on gastric emptying and produces only a weak aversion, at best, to the barium meal. However, while treating rats with insulin reverses the radiation-induced delay in gastric emptying [59], it does not disrupt the acquisition of a radiation-induced CTA [16].

A second approach to evaluating a possible role for direct gastrointestinal effects in CTA learning has involved sectioning the vagus nerve. The vagus constitutes the most extensive afferent source from the gut to the central nervous system [88] and has been implicated in the regulation of a wide range of visceral homeostatic functions [79, 80, 137]. If disruption of gastric function is the UCS for the acquisition of a radiation-induced CTA and this information is relayed to the brain by neural pathways from the stomach, then sectioning the vagus might be expected to produce some changes in the acquisition of the CTA [22,80]. However, Rabin, Hunt and Lee [105] found that subdiaphragmatic vagotomy in rats did not disrupt the acquisition of a CTA following exposure to either 200 rad whole-body or body-only irradiation. The results obtained with taste aversions produced by exposure to ionizing radiation generally parallel those obtained with drugs. In general, vagotomy has no effect on the acquisition of taste aversions induced by systemic toxins such as apomorphine, LiCl or ethanol [68, 69, 80, 105]. While these studies do not eliminate the possibility that the relevant information for CTA learning may be carried from the gut to the central nervous system by alternate pathways (e.g., splanchnic), it does not seem likely that a radiation-induced change in gastric function mediated by the vagus nerve, which provides the most extensive afferent source, serves as the proximate UCS for CTA learning following exposure to radiation.

In contrast, the emetic response to gastric irritation produced by intragastrically administered copper sulfate is greatly attenuated by vagotomy [137]. Concordant with this finding is the report that subdiaphragmatic vagotomy in rats disrupts CTA acquisition following intragastric and intraperitoneal copper sulfate, but not following intravenous administration [24]. While this finding would suggest that vagally-mediated changes in gastrointestinal function can play a role in CTA learning, Rabin *et al.* [105,109] have been unable to replicate this finding. Although more work is needed to resolve this discrepancy, the evidence suggesting a direct gastrointestinal involvement in CTA learning is not compelling.

Role of Humoral and Neural Mechanisms

In contrast to the above, there is good support for the hypothesis that exposure to ionizing radiation causes the release of a humoral factor, which in turn serves to mediate the acquisition of a CTA. Using a standard CTA paradigm, Hunt *et al.* [62] exposed one member of a parabiotic pair of rats to 360 rad of ionizing radiation while the other member of the pair was shielded. When tested for a saccharin preference, the shielded member of the pair showed a significant aversion to the saccharin solution. Since the parabiotic pair share a common blood supply, the inference is that some blood transferable humoral factor is produced in the irradiated member that can act as a UCS for the shielded member. There appears to be a dose/response relationship between the dose of radiation and the release of the humoral factor because the strength of the aversion produced in the shielded member of the parabiotic pair varies as a function of the dose to which the unshielded member is exposed [63].

Additional support for the hypothesis that a radiation-released humoral factor which serves to mediate CTA learning following exposure to ionizing radiation comes from the observation that a CTA can be produced in rats by injecting them with serum from rats that have been previously exposed to radiation [43]. However, caution must be used in interpreting the results of this experiment because the donor rats were subjected to extreme doses of radiation (30000 rad) and because the recipient rats were given injections of 12 ml of serum in 3 injections separated by 15 min each on 4 separate experimental days. This procedure is so different from the standard procedures for producing a CTA that the degree to which we can generalize from these results to the more typical experiment is not certain.

Another line of evidence that is consistent with the hypothesis of humoral mediation of the radiation-induced CTA comes from studies of the effect of area postrema lesions on CTA learning. The area postrema is the chemoreceptive trigger zone for emesis which functions to monitor the blood and cerebrospinal fluid for toxins [9]. Lesions of the area postrema disrupt the emetic response to a variety of blood-borne toxins [9] as well as to intraventricular histamine [6]. Similarly, lesions of the area postrema disrupt the emetic response to ionizing radiation in monkeys [12] and in dogs [20], suggesting that a humoral factor mediates the emetic response to irradiation. This conclusion is limited by the observation that area postrema lesions have been reported to have no effect on emesis produced by whole body irradiation in the cat [8]. However, more recent work indicates that area postrema lesions are effective in disrupting emesis in cats exposed to body-only radiation (Rabin, Hunt, Chedester and Lee, in preparation).

As with blood-borne emetic stimuli, lesions of the area postrema disrupt CTA acquisition to systemically-administered drugs. Area postrema lesions have been shown to attenuate CTA learning following intraperitoneal injections of methylscopolamine [4], LiCl [103,114] and histamine [103], as well as following an intravenous injection of copper sulfate [22]. The area postrema thus seems to mediate CTA learning for a particular class of unconditioned stimuli that are apparently related in some manner to emesis because the area postrema lesions do not disrupt the CTA produced by injections of amphetamine [4,114]. A similar distinction between LiCl and amphetamine as representing different classes of unconditioned stimuli for CTA learning has been made by Parker [95] based upon the observation of different nonconsummatory behavioral responses produced by treatment with these stimuli.

It therefore seems that there are two classes of UCS for CTA learning: one mediated by the area postrema and the other which does not depend upon the integrity of the area postrema. The CTA produced by exposure to ionizing radiation, for the most part, falls within the class of UCS that is mediated by the area postrema. Lesions of the area postrema produce an equivalent attenuation of taste aversions produced by exposure to gamma radiation and by injection of LiCl and histamine [93,101]. Also consistent with this hypothesis is the observation that lesions of the area postrema after the initial pairing of a novel sucrose solution with either radiation or LiCl on the conditioning day has no effect on the subsequent recall of the CTA [107]. This observation further confirms the function of the area postrema as a transfer point by which information about potential toxins in the blood and

cerebrospinal fluid is transmitted into the central nervous system.

As indicated above, a comparison of aversions produced by partial-body exposures indicates that irradiation of the body-only is more effective in producing a CTA than is irradiation of the head-only [40, 126]. This finding raises the possibility that taste aversions produced by head- and body-only exposures may involve different mechanisms. This possibility was evaluated in an experiment comparing the effects of area postrema lesions on the acquisition of a CTA produced by head- or body-only exposure [106]. Lesions of the area postrema of rats exposed to body-only radiation produced a complete disruption of CTA learning. In contrast, area postrema lesions in rats exposed to head-only radiation, while producing a significant attenuation of the CTA, did not prevent the occurrence of a significant reduction in test day sucrose preference compared to conditioning day preference. These results indicate that the acquisition of a CTA following partial-body exposures is mediated by the area postrema and also involves additional mechanisms not dependent upon the integrity of the area postrema. A direct effect of radiation on the brain mediating the acquisition of a CTA would be consistent with studies indicating changes in electrocortical activity [24, 86, 87], in seizure thresholds [88,97], and in sodium channel function [140] at radiation doses of less than 300 rad.

Role of Central Neurotransmitters

So far, there is little indication what brain mechanisms may mediate radiation-induced CTA learning in the absence of the area postrema. One possible approach to determining potential mechanisms would be to examine the effects of irradiation on central neurotransmitters. For example, neurochemical studies have, in fact, indicated that exposing an organism to ionizing radiation can affect biogenic amines in the brain [65].

A number of neurobehavioral studies have been undertaken in an attempt to determine the mechanisms of CTA learning produced by a variety of unconditioned stimuli. Most of these studies use lesions of various areas of the brain and drugs that modify the actions of neurotransmitters. The relationship of these studies to the mechanisms of radiation-induced taste aversions is not clear, since they generally have involved unconditioned stimuli other than radiation. However, based on the discussions in previous sections of this review, it may be possible to infer potential mechanisms of radiation-induced taste aversions through the actions of unconditioned stimuli that seem to act in a manner similar to radiation. One way to group these stimuli is by the ability of lesions of the area postrema to block specific aversions. Since both radiation- and LiCl-induced aversions are prevented by area postrema lesions, actions of lithium relative to the development of a CTA might have some bearing on how radiation induces a CTA.

The manipulation of the actions of neurotransmitters has been a major means by which possible mechanisms underlying CTA learning have been examined. These manipulations have been accomplished either by administering drugs that either facilitate or suppress the activity of a given transmitter or by applying selective lesions to areas of the brain that send afferents containing that transmitter or contain the synaptic endings. Most of the research, though limited, has focused on the biogenic amines that include the catecholamines, dopamine and norepinephrine, and the indoleamine, serotonin. A few studies have appeared examining cholinergic mechanisms.

One difficulty inherent in this approach, however, is the possible confounding of the processes that lead to the initiation of the behavior with those that lead to the association of the CS with the UCS or to the expression of the behavior. Since the acquisition of a response can only be demonstrated through its subsequent performance, the failure of an organism to show a CTA following neurochemical manipulation of the brain may reflect a deficit in either process. Since the present concern is with the mechanisms responsible for the initiation of the CTA response, care must be taken to separate out these various processes that lead to the performance of a learned response. Ideally, the experiment should be designed to show that a given manipulation disrupts CTA learning to a class of unconditioned stimuli presumed to have a similar mechanism of action while having no effect on the acquisition of a CTA induced by stimuli presumed to have a different mechanism of action.

This approach has been utilized in the comparison of LiCl and amphetamine as unconditioned stimuli for taste aversion learning. Lesions of the area postrema disrupt the acquisition of a CTA produced by injection of LiCl and methylscopolamine, but have no effect on an aversion produced by amphetamine [4,114]. Conversely, manipulation of catecholaminergic systems, either by injection of 6-hydroxydopamine [115,135] or by lesions of the dorsolateral tegmentum [139] attenuate a CTA produced by injection of amphetamine, but have no effect on the acquisition of a CTA following injection of LiCl. Because these experiments show that the effects of manipulation of catecholaminergic systems on CTA learning are restricted to a single class of unconditioned stimuli, it would suggest that the effects of manipulation of these systems are on the mechanisms responsible for the initiation of the response and not on the processes responsible for the association or performance of the response.

One transmitter whose activity correlates with the development of an LiCl-induced CTA is serotonin. Various manipulations that alter serotonergic activity can modify the magnitude of the CTA. Lesions of the median raphe nucleus, but not the dorsal raphe nucleus prior to conditioning enhance the LiCl-induced CTA [76]. On the other hand, pretreatment of either raphe-lesioned or unlesioned animals are pretreated before conditioning with 5-hydroxytryptophan, the precursor of serotonin, or with inhibitors of serotonin uptake results in the acquisition of an attenuated CTA [77,78]. Since medial raphe lesions deplete serotonin in limbic structures such as the hippocampus and septum, the results of these studies are interpreted as indicating that the role of serotonin may be to modulate the perceived intensity of the toxic stimulus.

In general, there is little evidence for a role of catecholamines in radiation- or LiCl-induced CTA learning. Blockade of catecholamine synthesis or dopaminergic receptors does not alter the subsequent development of a CTA [99,122]. Also, as indicated above, depletion of forebrain norepinephrine with the neurotoxin 6-hydroxydopamine or electrolytic lesions of the dorsolateral tegmentum are ineffective [81, 139]. On the other hand, infusions of beta-adrenergic agonists and antagonists into the ventricular system of the brain have been reported to modify the development of LiCl-induced taste aversions. The agonist enhances the CTA and the antagonist reduces it [72]. Because similar infusions into the lateral hypothalamus can alter the aversiveness of

certain tastes, these treatments may be related to the magnitude of an animal's response to taste. Also, because lesions of the amygdala produce a nonselective disruption of CTA learning produced by X-irradiation [32] as well as to both LiCl and amphetamine injection [54], and because the depletion of norepinephrine produced by injection of 6-hydroxydopamine into the basolateral amygdala also disrupts CTA learning [11], it may be that catecholamines are more related to the association of the CTA response to a CS than to the nature of the UCS.

Results from experiments studying the effect of drugs that block acetylcholine receptors have depended upon the doses used. With low doses of atropine (0.6 mg/kg, SC) or scopolamine (0.05–1.0 mg/kg, SC), the development of a radiation- or LiCl-induced CTA is not altered [37,125]. After higher doses of atropine (15 mg/kg, SC or 100 mg/kg, IP), radiation- and LiCl-induced taste aversions are attenuated [29,52]. However, interpretation of these results is further complicated by the observation that treatment with atropine sulfate (25 mg/kg, IP) itself produces a CTA [98].

Although its relevance to radiation-induced CTA learning has yet to be directly established, endogenous opioids have been implicated as mediating some of the behavioral changes observed following exposure to ionizing radiation [83,84]. Mickley [83] has reported that treatment with naloxone prevents the occurrence of a radiation-induced stereotypic hyperactivity in C57BL/6J mice that is similar to the behavioral response of these mice to treatment with morphine. Also, morphine-tolerant rats show a smaller radiation-induced performance decrement than do non-tolerant rats [84]. Similar results have been reported by Tesky and Kavaliers [132] who observed a radiation-induced analgesia in CF-1 mice which could be reversed by treatment with naloxone. Because treatment with morphine produces a CTA that can be attenuated by treatment with naloxone [74,134], it may be that endogenous opioids play a role in the acquisition of a radiation-induced CTA. However, Rabin and Hunt (unpublished manuscript) found that pretreating rats with a single injection of naloxone did not attenuate the acquisition of a radiation-induced CTA.

From this discussion, there is no clear role for the major transmitters in initiating a CTA induced by radiation- or drug-released toxins acting through the area postrema. The effects observed after transmitter manipulation appear to be related more to the expression of the CTA.

CONCLUSIONS

Overall, the research reviewed in this report would be consistent with the hypothesis that there are at least two classes of unconditioned stimuli that can lead to the acquisition of a CTA. The first class consists of those unconditioned stimuli, such as amphetamine, that do not require the mediation of the area postrema for CTA learning. In the second class, there are those stimuli, such as LiCl, which require the mediation of the area postrema for the acquisition of a CTA. For the most part, radiation, as a UCS for CTA learning, seems to belong to the second class of stimuli.

The area postrema is one of a group of circumventricular organs that is characterized by a relatively weak blood/brain barrier [28]. As such, it may be assumed that the role of the area postrema in CTA learning is to transfer to the central nervous system information about the presence of toxins in blood and cerebrospinal fluid when those toxins cannot cross the blood/brain barrier [107]. This hypothesis would be consistent with the observation that lesions of the area postrema disrupt CTA learning following injection of methylscopolamine, which cannot cross the blood/brain barrier, but have no effect on CTA learning when the UCS is a drug such as amphetamine, which can cross the barrier [4,114]. However, this hypothesis does not account for the disruption of an LiCl-induced CTA by area postrema lesions because LiCl does cross the blood/brain barrier [25]. Therefore, other factors, in addition to the ability of a substance to cross the blood/brain barrier, might determine whether or not the area postrema plays a necessary role in the acquisition of a CTA. It may be that the central effects of LiCl, unlike those of amphetamine, are not relevant for the acquisition of a CTA.

While the data indicate that activation of the area postrema is not a necessary condition for CTA learning, there are some very limited data which suggests that it might be a sufficient condition. In the cat, but not in the rat, the cardiovascular effects of angiotensin II are mediated by the area postrema [121]. In agreement with these findings is the observation that injection of angiotensin II produces changes in the activity of single units in the area postrema of the cat [10], but has no such effects in the rat [13]. Concordant with the electrophysiological data on the area postrema is the observation by Rabin *et al.* [111] that injection of angiotensin II will produce a CTA in cats, but not in rats. To more fully evaluate this possibility that activation of the area postrema may constitute a sufficient condition for CTA learning, however, would require additional electrophysiological studies monitoring the response of area postrema neurons to toxins that do not cause a CTA.

One other question concerns the specific nature of the UCS. The data reviewed in previous sections do not provide clear evidence as to whether the potential toxicity of a certain class of unconditioned stimuli, such as ionizing radiation and LiCl, is the proximal antecedent condition for CTA learning. Because a CTA can be produced by nontoxic stimuli that organisms will self-administer, a UCS-produced illness cannot be considered a necessary condition for CTA learning. Even where a toxic UCS is utilized, the data do not provide unequivocal support for the common assumption that a stimulus-induced illness is a sufficient condition for CTA learning. This is true not only for a UCS such as LiCl, which produces overt signs of distress, but even more so for exposure to ionizing radiation, which produces no overt changes in unrestrained behavior. It may be that radiation is able to produce a CTA because it activates the neural circuits associated with illness even in the absence of the experience of the illness by the awake organism [100]. Alternatively, it may be, as suggested by Gamzu [38], that the basis for taste aversion learning lies in the novelty of the treatment-induced state: that any treatment will produce a CTA as long as it produces a novel, discriminable state within the organism. In this view, ionizing radiation is able to lead to CTA learning because irradiation produces a discriminable change in nervous system activity. The potentially toxic character of the radiation UCS, or any other UCS such as LiCl, is not directly relevant to the CTA learning as long as that UCS is capable of producing a discriminably different state. As such, the UCS-produced illness may not be the direct antecedent cause of the CTA, but may rather simply be an unavoidable side-effect of the treatment that produces such a novel state.

The final question concerns the nature of the interaction between the UCS and the area postrema. When a CTA is

acquired following treatment with a systemic toxin, such as LiCl, which involves the mediation of the area postrema, an implicit assumption is that the toxin exerts direct effects on neuronal activity of the area postrema leading to CTA learning. This assumption, however, might not be correct. Smith [123] reported that injection of LiCl directly into the fourth ventricle, unlike systemically administered LiCl, did not produce a CTA. The implication of this finding is that CTA learning following systemic (intraperitoneal or intragastric) treatment with LiCl does not result from a direct action of lithium on area postrema neurons, but rather that systemic treatment with LiCl causes the release of an endogenous mediator to which the area postrema is sensitive. Thus, the LiCl-induced CTA, like the radiation-induced CTA, may depend upon a treatment-released humoral factor which serves as the proximate UCS for CTA learning. It is interesting to speculate that, because manipulations which affect LiCl-induced CTA learning also affect the radiation-induced CTA, the same endogenous humoral factor mediates CTA learning following treatment with either UCS; or, indeed, any UCS that requires the mediation of the area postrema.

Electrophysiological studies have shown that the area postrema is sensitive to a variety of endogenous peptides. Working with dogs, Carpenter and his coworkers [17,18] have reported that iontophoretic application of a variety of peptides causes changes in the activity of area postrema neurons and that systemic treatment with these same peptides causes emesis. In rats, treatment with the gastrointestinal hormone cholecystokinin may produce a CTA ([27,33], but see [48] for contrary data) that is mediated by the area postrema [133]. A CTA has also been reported to result from repeated systemic injection of arginine vasopressin [34]. Whether any of these peptides can, in fact, serve as the factor which is the proximal UCS for CTA learning following exposure to ionizing radiation or following systemic treatment with LiCl remains to be established.

It is, however, clear that the CTA, as a CR to a CS associated with toxic consequences to the organism, has definite implications for the survival of the organism. Given the wide range of unconditioned stimuli which can elicit a CTA, it is unlikely that the area postrema would have evolved specific receptors for each potential toxin. Rather, it is more likely that a class of toxic stimuli produce a series of similar effects resulting in the release of an endogenous factor. This factor may alter the activity of neurons within the area postrema with the consequent development of a CTA. Radiation is capable of functioning as a UCS for CTA learning because it too is capable of causing the release of this humoral factor. Ionizing radiation is, therefore, just one member of a class of environmental toxins that induce a CTA through the release of some endogenous factor affecting the activity of the area postrema. The validity of this hypothesis and the definition of a potential endogenous factor remain to be established by further research.

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